SHORT REPORT

Pesticide use and incident hyperthyroidism in farmers in the Agricultural Health Study

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► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/oemed-2018-105518).

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Received 5 October 2018
Revised 27 December 2018
Accepted 12 January 2019
Published Online First 25 February 2019

To cite: Shrestha S, Parks CG, Goldner WS, *et al. Occup Environ Med* 2019;**76**:332–335.

ABSTRACT

Background Few studies have evaluated associations between pesticides and hyperthyroidism.

Objective We evaluated associations between specific pesticides and incident hyperthyroidism in private pesticide applicators in the Agricultural Health Study.

Methods We used Cox proportional hazards models to estimate HRs and 95% CIs for associations between pesticide use at enrolment and hyperthyroidism (n=271) in 35 150 applicators (mostly men), adjusting for potential confounders.

Results Ever use of several pesticides (organophosphate insecticide malathion, fungicide maneb/mancozeb, herbicides dicamba, metolachlor, and atrazine in overall sample and chlorimuron ethyl among those ≤62 years) was associated with reduced hyperthyroidism risk, with HRs ranging from 0.50 (95% CI 0.30 to 0.83) for maneb/mancozeb to 0.77 (95% CI 0.59 to 1.00) for atrazine. Hyperthyroidism risk was lowest among those with higher intensity-weighted lifetime days of using carbofuran and chlorpyrifos (p_{trend} ≤0.05).

Conclusions Observed associations between pesticides and decreased risk of hyperthyroidism warrant further investigation.

Key messages

What is already known about this subject?
- Some pesticides have been shown to have thyroid-disrupting properties.
- The only epidemiological studies of pesticides and hyperthyroidism come from the Agricultural Health Study (AHS).
- Both prevalent and incident hyperthyroidism were associated with use of specific pesticides among spouses of farmers in the AHS.

What are the new findings?
- We did not detect evidence of increased hyperthyroidism risk associated with pesticide use by AHS farmers, but found reduced risk in those exposed to some pesticides.

How might this impact on policy or clinical practice in the foreseeable future?
- These findings are some of the earliest data on pesticide use and hyperthyroidism.
- Findings suggest the need for future studies of possible mechanistic differences in risk between men and women exposed to pesticides and for better understanding of how pesticides affect thyroid function.

INTRODUCTION

Several studies have reported links between pesticides and subtle alterations in thyroid biomarkers including thyroid hormones and thyroid autoantibodies in euthyroid individuals.[1 2] Relatively few studies have investigated pesticides and clinical thyroid conditions, hyperthyroidism in particular. We know of only two investigations of the link between pesticides and hyperthyroidism, both conducted in female spouses of private pesticide applicators in the Agricultural Health Study (AHS).[3 4] Identifying risk factors for hyperthyroidism can have important implications given its association with adverse outcomes including cardiovascular disease, poor bone health and overall poor health-related quality of life.[5]

The AHS is a prospective cohort study of licensed private pesticide applicators (mainly farmers and hereafter referred to as farmers) and their spouses from North Carolina and Iowa.[6] Recently, we reported elevated risk of hypothyroidism in farmers exposed to several organochlorine and organophosphate insecticides and phenoxy herbicides.[7] Here, we report associations between pesticide use and incident hyperthyroidism in AHS farmers.

METHODS

Study population

Between 1993 and 1997, 52 394 farmers enrolled in the AHS by completing an enrolment questionnaire.[6] Those enrolled received an additional take-home questionnaire; 22 916 enrolees (44%) returned it. Participants were contacted again in 1999–2003, 2005–2010 and 2013–2016. All questionnaires can be accessed from https://aghealth.nih.gov/collaboration/questionnaires.html.

Pesticide use

The enrolment questionnaire asked about ever-use of 50 pesticides, and duration (years) and frequency (average days per year) of use for 22 of them. A take-home questionnaire asked about duration and frequency of use for the remaining 28. Responses to questions about pesticide use practices were used to create exposure intensity weights.[8] We multiplied

duration and frequency of use to obtain lifetime days of use for each pesticide which was then weighted by exposure intensity to obtain intensity-weighted lifetime days (IWLDs) of use. Here, we report results for ever-use and IWLDs categorised into three groups (never use, ≤median and >median days among users).

Hyperthyroidism

Participants were asked about doctor-diagnosed thyroid diseases in all surveys. Follow-up interviews obtained information including disease subtypes and age at diagnosis. Some participants reported having multiple thyroid disease types. This could be because hypothyroidism can develop after hyperthyroidism treatments or naturally, and vice versa, or could reflect misreporting. Therefore, we created decision rules to define 'hypothyroidism' and 'hyperthyroidism'. Briefly, when participants' hyperthyroidism diagnosis preceded hypothyroidism, they were considered to have developed hyperthyroidism first, with the assumption that their hypothyroidism likely resulted from treatment. We excluded individuals whose hyperthyroidism developed after hypothyroidism (as this order happens infrequently). Details are described elsewhere.[7]

We attempted to validate hyperthyroid disease by obtaining medical records (details described elsewhere[4 7]) but were not very successful. First, among participants who had self-reported hyperthyroidism in the past, most, when contacted again, confirmed that they had thyroid disease, but only about a half specifically affirmed a diagnosis of hyperthyroidism, although about 95% were taking exogeneous thyroid hormones (as would be expected following hyperthyroidism treatment including thyroid ablation via radiation or surgery). Second, we were not successful in reaching the diagnosing physician in most cases; because individuals with treated hyperthyroidism were currently taking medications for hypothyroidism, information from current physician's offices was likely incomplete, resulting in validation of only 32% of hyperthyroidism self-reports by medical records. Nonetheless, we used information from those who did confirm hyperthyroidism or whose physicians could document the diagnosis in sensitivity analyses as described below.

Statistical analysis

We assessed associations between baseline covariates and hyperthyroidism using logistic regression. We used Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between pesticides and hyperthyroidism; these models used attained age as the time scale with left truncation at enrolment and adjusted for sex, education, state and smoking. Person-time accrued until the earlier of a hyperthyroidism diagnosis or a censoring event (hypothyroidism diagnosis, death, loss to or end of follow-up). We allowed hazards to vary by the median attained age (62 years) for analyses of specific pesticides that did not meet the proportional hazards assumption. We also repeated analyses for ever-use of pesticides excluding female applicators and adjusting for pesticides that were correlated with Spearman correlation coefficient ≥0.40. To minimise bias associated with disease misclassification, we conducted an additional analysis restricted to cases who reported having hyperthyroidism at least twice across surveys, or whose diagnosis was reaffirmed in a validation screener or confirmed by medical records (68 hyperthyroidism cases satisfied this case definition). We required at least 10 cases in each exposure category for the main analysis and at least five cases in the stricter case analysis because of limited sample size. Analyses were performed using SAS V. 9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

We restricted analysis to 38 698 farmers who completed at least one follow-up survey. After excluding prevalent and unknown thyroid diseases, inconsistent responses and those without complete covariate information, our final analytical sample included 35 150 participants (34 050 without thyroid disease, 271 with hyperthyroidism and 829 with hypothyroidism who were censored at age of diagnosis). For analyses of IWLD for the 28 pesticides whose frequency and duration of use relied on the take-home questionnaire, the final analytical sample was 17 832 (137 with hyperthyroidism and 506 with hypothyroidism).

Those who reported hyperthyroidism were older, less likely to consume alcohol, and more likely to be female and to have ever smoked (online supplementary table 1). We detected significantly lower risk of hyperthyroidism among those who ever used the organophosphate malathion, the fungicide maneb/mancozeb, and the herbicides metolachlor, dicamba and atrazine in the overall sample and chlorimuron ethyl among those ≤62 years (table 1). Risk was also lower for the organophosphate phorate; the fungicides benomyl and chlorothalonil; and the herbicides butylate and paraquat ($p<0.10$). Risk of hyperthyroidism was elevated for imazethapyr among those aged >62 years ($p=0.12$). The results were qualitatively similar when female applicators were excluded (except no elevated risk was detected for imazethapyr among those aged >62 years) or when adjusted for correlated pesticides (except the HR for benomyl was attenuated) (online supplementary tables 2 and 3). Under our stricter case definition, most associations were in the same direction but with generally imprecise CIs. Online supplementary table 4 presents the results for IWLDs. We detected the greatest risk reduction for those exposed to more than median IWLDs for carbofuran, chlorpyrifos, metolachlor and pendimethalin.

DISCUSSION

We observed significantly reduced hyperthyroidism risk among applicators exposed to several pesticides—contrary to the findings in female AHS spouses. In AHS spouses, hyperthyroidism risk was elevated in those who ever used several pesticides including the fungicide maneb/mancozeb and the herbicide metolachlor.[4]

We can offer several potential explanations for why we saw reduced hyperthyroidism risk for some of these pesticides. First, a likely explanation could be possible confounding or effect modification by other common non-pesticide farming exposures. Second, some of these pesticides, depending on exposure intensity, may elicit non-monotonic thyroid responses, and the higher pesticide exposure in our farmers resulted in hypothyroidism first, reducing the participant pool for development of hyperthyroidism. Unfortunately, prior human studies on pesticides and hyperthyroidism are limited to the investigations in AHS spouses, and not much can be gathered from existing cross-sectional studies examining levels of circulating thyroid-stimulating hormone and thyroid hormones regarding pesticides' potential to elicit both hyperthyroid-like and hypothyroid-like effects. As for differential association by espousal status, as 98% farmers were male, it is possible that such associations could be explained by sex-related differences, specifically factors that might predispose women to have higher thyroid disease burden (for instance, parity, oestrogen).[9] Because there were few female applicators, we lacked power to evaluate sex-specific differences directly.

Table 1 Ever-use of pesticides and hyperthyroidism risk

	Overall sample (n=35 150)*		Stricter case definition (n=34 463)†	
Pesticide	Exposed cases	HR (95% CI)‡	Exposed cases	HR (95% CI)§
Organochlorine insecticide				
Aldrin	43	0.82 (0.57 to 1.16)	8	0.73 (0.33 to 1.60)
Chlordane	68	0.92 (0.69 to 1.24)	13	0.73 (0.39 to 1.39)
DDT	73	0.98 (0.71 to 1.34)	12	0.80 (0.40 to 1.60)
Dieldrin	18	0.99 (0.60 to 1.62)	–	–
Heptachlor	39	0.94 (0.65 to 1.36)	–	–
Lindane	45	0.93 (0.67 to 1.30)	–	–
Toxaphene	31	0.74 (0.50 to 1.09)	7	0.70 (0.31 to 1.58)
Carbamate insecticide				
Aldicarb	26	0.84 (0.54 to 1.30)	5	0.61 (0.23 to 1.60)
Carbaryl (overall)	143	0.81 (0.62 to 1.07)	–	–
≤62 years¶	–	–	27	0.96 (0.51 to 1.79)
>62 years¶	–	–	7	0.43 (0.15 to 1.23)
Carbofuran	58	0.79 (0.59 to 1.07)	10	**0.51 (0.26 to1.01)**
Organophosphate insecticide				
Chlorpyrifos	98	0.85 (0.66 to 1.09)	26	0.85 (0.52 to 1.39)
Coumaphos	17	0.79 (0.48 to 1.29)	–	–
Diazinon	88	1.05 (0.80 to 1.39)	–	–
Dichlorvos	23	0.96 (0.62 to 1.49)	5	0.76 (0.30 to 1.93)
Fonofos	52	1.13 (0.82 to 1.57)	11	0.86 (0.43 to 1.70)
Malathion	158	**0.68 (0.52 to 0.88)**	37	**0.56 (0.33 to 0.94)**
Parathion	39	0.94 (0.66 to 1.34)	9	0.87 (0.42 to 1.81)
Phorate	63	0.75 (0.56 to 1.02)	13	0.56 (0.30 to 1.07)
Terbufos	84	0.91 (0.69 to 1.20)	16	**0.54 (0.30 to 0.98)**
Pyrethroid insecticide				
Permethrin (animals)	31	1.09 (0.74 to 1.61)	6	0.67 (0.28 to 1.60)
Permethrin (crops)	24	0.73 (0.48 to 1.12)	8	0.95 (0.45 to 2.01)
Fumigant				
Carbon tetrachloride/ carbon disulfide 80/20 mix	14	0.96 (0.56 to 1.66)	–	–
Aluminium phosphide	11	0.97 (0.53 to 1.78)	–	–
Ethylene dibromide	11	1.14 (0.62 to 2.11)	–	–
Methyl bromide	50	0.91 (0.64 to 1.30)	12	0.85 (0.41 to 1.73)
Fungicide				
Benomyl	21	0.63 (0.40 to 1.02)	6	0.75 (0.31 to 1.85)
Captan ≤62 years¶	11	0.62 (0.33 to 1.15)	–	–
>62 years¶	10	1.08 (0.56 to 2.10)	–	–
Chlorothalonil	16	0.61 (0.36 to 1.03)	5	0.76 (0.29 to 1.97)
Maneb/mancozeb	17	**0.50 (0.30 to 0.83)**	6	0.77 (0.31 to 1.91)
Metalaxyl	64	0.92 (0.67 to 1.27)	15	0.92 (0.47 to 1.79)
Herbicide				
Alachlor	120	0.88 (0.68 to 1.14)	32	1.03 (0.61 to 1.75)
Butylate	62	0.76 (0.56 to 1.02)	14	0.59 (0.32 to 1.08)
Chlorimuron ethyl (overall)	–	–	19	0.80 (0.46 to 1.40)
≤62 years¶	44	**0.70 (0.49 to1.00)**	–	–
>62 years¶	30	1.16 (0.75 to 1.80)	–	–
Dicamba	100	**0.74 (0.55 to1.00)**	–	–
EPTC	37	0.84 (0.59 to 1.21)	7	0.55 (0.25 to 1.23)
Glyphosate	210	1.06 (0.79 to 1.43)	59	1.81 (0.89 to 3.70)
Imazethapyr (overall)		–	26	1.23 (0.66 to 2.29)
≤62 years¶	56	0.89 (0.61 to 1.29)	–	–
>62 years¶	38	1.43 (0.91 to 2.24)	–	–
Metolachlor	88	**0.75 (0.57 to0.99)**	22	0.68 (0.39 to 1.16)
Paraquat	50	0.75 (0.54 to 1.05)	12	0.67 (0.34 to 1.32)

continued

Table 1 continued

Pesticide	Overall sample (n=35 150)*		Stricter case definition (n=34 463)†	
	Exposed cases	HR (95% CI)‡	Exposed cases	HR (95% CI)§
Pendimethalin	102	0.97 (0.75 to 1.26)	26	0.94 (0.56 to 1.57)
Petroleum oil	102	0.89 (0.68 to 1.16)	31	1.20 (0.71 to 2.03)
Trifluralin	123	1.05 (0.80 to 1.38)	34	1.21 (0.70 to 2.10)
2,4-D (overall)	188	0.86 (0.65 to 1.14)	–	–
≤62 years¶	–	–	40	1.09 (0.56 to 2.11)
>62 years¶	–	–	8	**0.31 (0.11 to 0.83)**
2,4,5T	56	1.01 (0.74 to 1.38)	9	0.62 (0.30 to 1.29)
2,4,5T P	22	0.93 (0.60 to 1.45)	–	–
Atrazine	170	**0.77 (0.59 to1.00)**	45	0.82 (0.48 to 1.39)
Cyanazine	87	0.86 (0.64 to 1.16)	20	0.70 (0.39 to 1.27)
Metribuzin	101	0.96 (0.73 to 1.27)	22	0.66 (0.38 to 1.16)

Bold-face indicates p value≤0.05.

*Analysis with overall sample

†Analysis with cases restricted to those confirmed by a validation questionnaire or medical records or who reported having hyperthyroidism at least two times in surveys.

‡Adjusted for sex, education, state and smoking.

§Adjusted for education, state and smoking (as there were no female cases of hyperthyroidism).

¶HR allowed to vary by the median age (ie, 62 years) for pesticides for which proportional hazards assumptions were not met (p≤0.10)

DDT, dichlorodiphenyltrichloroethane; EPTC, S-ethyl dipropylthiocarbamate; 2,4-D, 2,4-Dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-Trichlorophenoxyacetic acid; 2,4,5T,P, 2-(2,4,5-trichlorophenoxy) propionic acid.

We relied on self-reports of hyperthyroidism. Although we attempted to validate diagnoses with medical records, we were not very successful. For the most part, we contacted current physicians who may not have been the diagnosing physician. Among those whose medical records were obtained, medical personnel confirmed only 32% of hyperthyroidism self-reports. If current staff reviewed only recent medical records, they may have missed and under-reported past hyperthyroidism diagnosis. In fact, during an unsystematic review of the small number of complete medical records that were sent to us, we encountered instances where hypothyroidism was specified in proximal medical records but earlier reports indicated hyperthyroidism. This observation offers some reason to believe that the failure to confirm the hyperthyroidism diagnoses was structural and not due to misreporting by participants. Furthermore, if those who reported hyperthyroidism actually had hypothyroidism, we would have expected results for hyperthyroidism in these farmers to be similar to those for hypothyroidism,[7] which was not the case.

We used self-reported pesticide information and did not account for pesticide use that occurred after enrolment, making the study vulnerable to bias from exposure misclassification. Still, pesticide use self-reports by AHS farmers are fairly reliable[10] and we used IWLDs that correlate better with urinary biomarkers compared with other cruder measures.[11] Further, we did not adjust for multiple comparisons and therefore some of our findings could be due to chance.

In summary, we observed decreased risk of hyperthyroidism among those exposed to certain pesticides in the AHS. This study's notable strengths include its large sample size, prospective design and comprehensive pesticide-use information. Nevertheless, several limitations necessitate careful interpretation of the findings.

Acknowledgements The authors thank Stuart Long from Westat for help with data management. AHS data releases AHSREL20150600, P1REL201209_00, P2REL20120900, P3REL20120900 and P4PreRel06172015 were used for this analysis.

Contributors All contributors meet the criteria for authorship.

Funding This work was supported by the Intramural Research Program of the National Institute of Health, National Institute of Environmental Health Sciences (Z01-ES-049030) and National Cancer Institute (Z01-CP-010119).

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Requests for data, including the data used in this manuscript, are welcome as described on the Study Website (https://www.aghealth.nih.gov/collaboration/process.html). Data requests may be made directly at www.aghealthstars.com; registration is required. The Agricultural Health Study is an ongoing prospective study. The data sharing policy was developed to protect the privacy of study participants and is consistent with study informed consent documents as approved by the NIH Institutional Review Board. Dr. Dale P Sandler is the NIEHS Principal Investigator of the Agricultural Health Study and is responsible for ensuring participant safety and privacy.

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